precise cut off in spirometric variables and control saturations below which a hypoxic stress test is desirable. If oxygen is prescribed then retention of carbon dioxide should be excluded.

The laboratory hypoxic test is a cheap and simple non-invasive test and is of practical value in determining fitness to fly in children with cystic fibrosis.

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Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors

Helen Lunde, Thomas Hedner, Ola Samuelsson, Jan Lötvall, Lennart Andrén, Lars Lindholm, Bengt-Erik Wiholm

Department of Clinical Pharmacology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden
Helen Lunde, *registrar in clinical pharmacology*
Thomas Hedner, *professor of clinical pharmacology*
Jan Lötvall, *senior registrar in clinical pharmacology*

Department of Nephrology, Sahlgrenska University Hospital, Gothenburg
Ola Samuelsson, *associate professor of nephrology*

Swedish Medical Products Agency, Uppsala, Sweden
Lennart Andrén, *associate professor*
Bengt-Erik Wiholm, *associate professor*

Health Sciences Centre, University of Lund, Dalby, Sweden
Lars Lindholm, *associate professor*

Correspondence to:
Dr Lunde.

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Abstract

***Objective*—To evaluate the occurrence of asthma and dyspnoea precipitated or worsened by angiotensin converting enzyme inhibitors.**

***Design*—Summary of reports of adverse respiratory reaction in relation to treatment with angiotensin converting enzyme inhibitors that were submitted to Swedish Adverse Drug Reactions Advisory Committee and to World Health Organisation's international drug information system until 1992. Sales of angiotensin converting enzyme inhibitors in Sweden were also summarised.**

***Subjects*—Patients receiving angiotensin converting enzyme inhibitors who reported adverse respiratory reactions.**

***Main outcome measures*—Clinical characteristics of adverse reactions of asthma, bronchospasm, and dyspnoea.**

***Results*—In Sweden 424 adverse respiratory reactions were reported, of which most (374) were coughing. However, 36 patients had adverse drug reactions diagnosed as asthma, bronchospasm, or dyspnoea. In 33 of these cases the indication for treatment with angiotensin converting enzyme inhibitors was hypertension, in only three heart failure. The respiratory symptoms occurred in about half of the patients within the first two weeks of treatment, and about one third needed hospitalisation or drug treatment. Dyspnoea symptoms occurred in conjunction with other symptoms from the airways or skin in 23 out of the 36 cases. In the WHO database there were 318 reports of asthma or bronchospasm, 516 reports of dyspnoea, and 7260 reports of cough in relation to 11 different angiotensin converting enzyme inhibitors.**

***Conclusion*—Symptoms of airway obstruction in relation to treatment with angiotensin converting enzyme inhibitors seem to be a rare but potentially serious reaction generally occurring within the first few weeks of treatment.**

Introduction

The angiotensin converting enzyme inhibitors were early suggested to represent a favourable drug in hypertensive patients with obstructive lung disease,[1] but coughing and possibly unspecific airway hyperreactivity are common in patients treated with these drugs.[2-5] Furthermore, single case reports indicate that asthma or bronchospasm may be caused by treatment with structurally different drugs such as captopril,[6] enalapril,[7] and lisinopril.[8] In order to evaluate the occurrence of dyspnoea, asthma, and bronchospasm in relation to angiotensin converting enzyme inhibitors, we summarised the results in available registers of adverse drug reactions.

Patients and methods

We obtained data from the Medical Products Agency and the Swedish Drug Information System as described previously.[9] On 4 February 1992 we looked for adverse respiratory reactions to angiotensin converting enzyme inhibitors reported during 1981-91 to the Swedish Adverse Drug Reactions Advisory Committee. We included only those reactions judged by the committee to be probably or possibly related to treatment with the drugs, and we obtained clinical reports on cases with aggravated asthma, bronchospasm, and dyspnoea for detailed scrutiny. We also determined the number of defined daily doses of angiotensin converting enzyme inhibitors sold in Sweden during 1981-91.

In addition, we summarised the reported adverse respiratory reactions related to treatment with angiotensin converting enzyme inhibitors that were submitted to the World Health Organisation Collaborating Centre for International Drug Monitoring up to 6 August 1992. We looked for the terms asthma, bronchospasm, aggravated bronchospasm, dyspnoea, and coughing as these are the preferred terms in the WHO's terminology of adverse drug reactions.[10] The information in the international drug information system at the WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden) is not homogeneous, at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The information in this paper expresses the judgment of the authors and does not represent the opinion of the WHO.

Results

A total of 1215 adverse drug reactions were judged to have been probably or possibly related to treatment with

angiotensin converting enzyme inhibitors in Sweden, of which 424 were adverse respiratory reactions. Coughing was the most common reaction (374/424, 88%) while the remaining 50 reactions were dyspnoea (19), aggravated asthma (11), bronchospasm (6), rhinitis (5), larynx oedema (4), nasal congestion (3), interstitial pneumonitis (1), and pleuritis (1).

Table I gives details of the 36 patients whose adverse drug reactions were dyspnoea, aggravated asthma, or bronchospasm. The patients (20 women and 16 men) had a mean age of 58·9 (range 29-82 years), and they had received angiotensin enzyme inhibitors either to treat hypertension (33 patients) or heart failure (three patients). Information about the time when the symptoms first occurred was available in 27 cases: 15 patients (42%) first experienced symptoms during the first week of treatment, and four (11%) first experienced symptoms during the second week. Three patients developed similar symptoms when rechallenged with a chemically different angiotensin converting enzyme inhibitor. Twelve patients also had cough, one had cough and angio-oedema, one reported cough, exanthema, and headache, two had suspected angio-oedema, and three had other skin reactions such as rash, urticaria, and flush. Two of the patients with aggravated asthma also had rhinitis.

One patient died, but the cause of death was not judged to be related to the drug treatment. In all other cases the symptoms rapidly improved on discontinuation of the angiotensin converting enzyme inhibitor. Five patients needed hospitalisation with bronchodilator treatment or ventilatory support, or both, and six patients were treated with antiasthmatic drugs in outpatient units. In 12 cases obstructive airway disease had been diagnosed, and eight of these patients were taking corticosteroids or β_2 agonists. Five patients had been taking β receptor antagonists for some time without any respiratory side effects before they started treatment with angiotensin converting enzyme inhibitors. In four of these cases both drugs were discontinued when the adverse reaction appeared, but in one case metoprolol treatment continued without any adverse respiratory reaction after enalapril was discontinued. Four patients had been taking non-steroidal

TABLE I—*Details of 36 Swedish patients with adverse respiratory reaction in relation to treatment with angiotensin converting enzyme inhibitor*

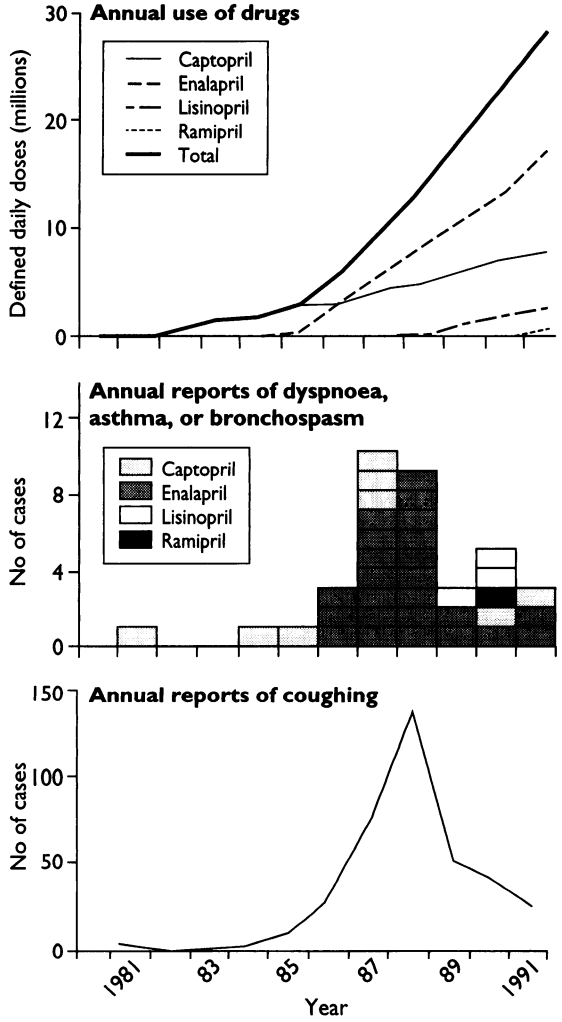
Sex and age (years)	Angiotensin converting enzyme inhibitor		Adverse drug reaction	Other treatment	Concomitant disease
	Drug (daily dose (mg))	Duration of treatment			
F41	Captopril (50-100)	6 months (3 weeks when rechallenged)	Dyspnoea, pruritus, exanthema	β Blockers	Renal hypertension
F56	Captopril (12·5)	1 day	Dyspnoea, urticaria	β Blockers, diuretics, β_2 agonist	Asthma, allergy, sarcoidosis, diabetes
F67	Enalapril (5)	2 weeks	Dyspnoea, flush	Insulin, diuretics, Ca^{2+} antagonist	Diabetes
F59	Enalapril (20)	NR	Dyspnoea, syncope, vertigo	β Blockers	
F74	Enalapril (2·5)	2 hours	Dyspnoea, bronchial obstruction	Diuretics, nitroglycerine, β blockers, aspirin, Ca^{2+} antagonist	Heart failure
F72	Enalapril (20)	~1 week (continued for 6 months)	Cough, dyspnoea	β Blockers, thyroxine, analgesics	Hypothyroidism
F61	Captopril (12·5)	~1 week (continued for 6 months)	Cough, dyspnoea	Thyroxine	Hypothyroidism
F82	Enalapril (10)	<1 week (continued for 6 months)	Cough, dyspnoea	Diuretics, β_2 agonist	
F37	Enalapril (5)	NR	Cough, dyspnoea		
M55	Enalapril (20-40)	2-3 weeks	Cough, dyspnoea, angio-oedema	Diuretics	
F53	Enalapril (20-40) or captopril (25-50)	3-4 weeks	Cough, dyspnoea		
F58	Enalapril (10)	5 days	Dyspnoea, angio-oedema		Diabetes, asthma
F70	Enalapril (20)	6 weeks	Cough, dyspnoea		
M57	Enalapril (10)	1-2 months	Cough, dyspnoea		
M54	Enalapril (20)	1 hour	Dyspnoea	β_2 Agonist, inhaled steroids, theophylline	Asthma
M74	Lisinopril (10)	1 day	Cough, dyspnoea	Ca^{2+} antagonist, nitroglycerine, NSAID	Angina pectoris, previous myocardial infection
M56	Enalapril (10)	NR	Aggravated asthma	NR	Obesity
F71	Ramipril (1·25)	1 hour	Dyspnoea, headache	Antidiabetics, anticoagulant, insulin	Diabetes
F50	Captopril (25)	2-3 weeks	Dyspnoea, cough		
F39	Captopril (50)	<1 day	Dyspnoea, pharynxoedema, dysphagia		
M57	Enalapril (20)	2-3 days	Aggravated asthma	NSAID as required	Bronchial asthma, uratic arthritis
F50	Enalapril (20)	2 days	Aggravated asthma, rhinitis		Bronchial asthma, bronchitis
M55	Enalapril (5-20)	1-2 weeks	Aggravated asthma, dyspnoea	Diuretics	Bronchial asthma
M62	Captopril (25-50)	2-3 days	Aggravated asthma	Ca^{2+} antagonist, β_2 antihistamine, theophylline, inhaled steroids	Bronchial asthma
M46	Enalapril (10-20)	1-2 weeks	Aggravated asthma, rhinitis	β_2 agonist, theophylline	Asthma, previous myocardial infarction
M29	Captopril (25)	~1 month	Aggravated asthma, dyspnoea	β_2 agonist, theophylline	Asthma
M53	Enalapril (10)	5-6 days	Aggravated asthma, dyspnoea	β_2 agonist, steroids	Asthma, bronchitis
F54	Enalapril (10)	<1 month	Cough, aggravated asthma		
M42	Enalapril (10)	~1 year	Asthma		Asthma as child
M73	Enalapril (10)	1½ years	Aggravated asthma	Quinidine, nitroglycerine, inhaled steroids, β_2 agonist, diuretics	Asthma, heart failure
F70	Captopril (37·5-75)	4-5 days	Bronchospasm	Diuretics, prazosin, inhaled steroids, theophylline	Renal artery, stenosis
M44	Enalapril (40)	~1 week	Asthma, bronchospasm	Diuretics	
M43	Enalapril (10-20)	1-2 weeks	Asthma, bronchospasm		
F82	Enalapril (5) or captopril (12·5)	2 days	Cough, bronchospasm	Digoxin, Ca^{2+} antagonists, diuretics, nitroglycerine, potassium	Heart failure
M59	Lisinopril (80-20)	~6 months	Cough, bronchospasm	Diuretics	
F63	Lisinopril (10) or captopril (25)	<1 week	Cough, headache, exanthema, bronchospasm		

NR=not reported, NSAID=non-steroidal anti-inflammatory drug.

TABLE II—*Annual number of possible cases of adverse respiratory reaction in relation to treatment with angiotensin converting enzyme inhibitors reported to WHO international drug information system*

Adverse reaction	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992*	Total
Coughing	4	15	34	28	174	573	1330	1439	1342	1494	716	111	7260
Asthma or bronchospasm	1	2	5	4	23	38	51	69	51	39	28	7	318
Dyspnoea	0	5	7	8	21	62	81	87	86	85	59	15	516
Total	5	22	46	40	218	673	1462	1595	1479	1618	803	133	8094

*Until 6 August.



Annual use of angiotensin converting enzyme inhibitors during 1981-91 in Sweden and concomitant reported cases of adverse respiratory reactions possibly related to use of these drugs

TABLE III—*Number of adverse respiratory reactions reported to WHO international drug information system until 6 August 1992 in relation to individual angiotensin converting enzyme inhibitors*

Drug	Coughing	Asthma, bronchospasm, or dyspnoea	Total
Captopril	2200	268	2468
Enalapril	3788	388	4176
Ramipril	36	7	43
Cilazapril	12	0	12
Benazepril	10	6	16
Lisinopril	1164	154	1318
Perindopril	30	6	36
Quinapril	16	2	18
Delapril	1	0	1
Fosinopril	1	3	4
Alacepril	2	0	2
Total	7260	834	8094

anti-inflammatory drugs for some time before they started treatment with angiotensin converting enzyme inhibitors, and three developed wheeze within one week of taking the enzyme inhibitor. One patient continued taking the anti-inflammatory agent without problems after the angiotensin converting enzyme inhibitor and the β receptor antagonist were discontinued.

The figure shows that the annual number of adverse respiratory reactions declined in Sweden after 1988 despite a continuous increase in the sales of angiotensin converting enzyme inhibitors. A similar pattern is shown by the yearly reports of adverse respiratory reactions to the WHO's international drug information system (table II). The reports concerned 11 different angiotensin converting enzyme inhibitors, and reports of cough were about nine times more common than those of asthma, bronchospasm, and dyspnoea (table III).

Discussion

Angiotensin converting enzyme is an unspecific dipeptide hydrolase with high capacity to degrade bradykinin and substance P to inactive metabolites. Inhibition of this enzyme will inhibit the degradation of these proinflammatory peptides.[11] In animal experiments it has been shown that inhibition of angiotensin converting enzyme will potentiate airway obstruction and increase airway plasma leakage in response to bradykinin and substance P.[12,13] Bradykinin can induce bronchoconstriction in asthmatic subjects.[14]

FORMER STUDIES

Only a few published case reports describe the development or exacerbation of asthmatic symptoms during treatment with angiotensin converting enzyme inhibitors.[6-8] A survey of coughing associated with captopril and enalapril treatment did not show any definite association of the cough reaction with asthma even though two of the 59 patients complained of wheeze and another showed exacerbation of asthma.[15] In a one year prescription event study of enalapril 2·9% of patients coughed, but there were no reports on asthma or dyspnoea.[16] There are few prospective controlled studies on the effects of angiotensin converting enzyme inhibitors on pulmomary function in asthmatic patients. In small, short term studies no overt changes in asthmatic symptoms or spirometric values emerged.[17-19]

In our study, however, we found several cases of angiotensin converting enzyme inhibitors apparently causing or worsening asthmatic symptoms and dyspnoea. Three of the patients developed adverse respiratory reactions with two different angiotensin converting enzyme inhibitors, suggesting that the reactions represented a class phenomenon rather than an allergic reaction to a specific substance. Interestingly, many of the patients had other symptoms such as cough, rhinitis, or angio-oedema as well as dyspnoea and wheeze, which may be explained by a local increase in proinflammatory peptides.

Spontaneous reporting of adverse experiences represents an important means of detecting infrequent adverse drug reactions but it does not provide information about the true incidence. A rough estimate of the risk, however, may be obtained by relating the

Clinical implications

- Coughing is a common and well recognised adverse reaction to angiotensin converting enzyme inhibitors whereas reports of asthma and bronchial hyperreactivity are conflicting
- This study examined the relation of spontaneously reported adverse respiratory reactions in Sweden to treatment with angiotensin converting enzyme inhibitors
- Coughing was reported 8-10 times more often than wheeze and dyspnoea, and in most cases asthmatic symptoms occurred together with coughing, rhinitis, angio-oedema, or other skin reactions
- In more than half of the cases wheeze or dyspnoea developed during the first two weeks of treatment
- Doctors should recognise asthma as a possible adverse reaction to angiotensin converting enzyme inhibitors

19 Swedish cases reported in 1987-8 to the calculated number of new prescriptions of angiotensin converting enzyme inhibitors in Sweden during this period. By extrapolating data from the Jämtland study and the prescription survey,[20] the number of new prescriptions can be roughly estimated as 117 200. Thus, a risk of one report for every 6200 new prescriptions can be calculated. This estimate is very rough, however, since both the numerator (actual reporting rate unknown) and the denominator (extrapolation from random samples) are associated with a considerable uncertainty.

CONCLUSION

Symptoms of airway obstruction caused by angiotensin converting enzyme inhibitors seem to be rare, but doctors should be aware of these reactions. Asthmatic patients may be more susceptible than others. Any suspicion of bronchospasm or aggravated asthma, even with patients who cough, should be carefully monitored and documented. Such adverse reactions usually require discontinuation of the angiotensin converting enzyme inhibitor.

The conclusions reached in this paper reflect the judgment of the authors and do not represent the opinion of the WHO.

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How effective is nicotine replacement therapy in helping people to stop smoking?

Jin Ling Tang, Malcolm Law, Nicholas Wald

Abstract

***Objective*—To assess the efficacy of nicotine replacement therapy in helping people to stop smoking.**

***Design*—Analysis of the results of 28 randomised trials of nicotine 2 mg chewing gum, six trials of nicotine 4 mg chewing gum, and six trials of nicotine transdermal patch.**

***Subjects and setting*—Subjects were self referred (responding to advertisements or attending anti-smoking clinics) in 20 trials and invited (general practice or hospital patients) in 20. Therapists in self referred trials were generally experienced in helping people stop smoking but not in invited trials.**

***Main outcome measure*—Efficacy was defined as difference in percentages of treated and control subjects who had stopped smoking at one year.**

***Results*—Efficacy was highly significant ($P < 0{\cdot}001$) for both gum and patch. Nicotine 2 mg chewing gum had an overall efficacy of 6% (95% confidence interval 4% to 8%), greater in self referred subjects than in invited subjects (11% *v* 3%). Efficacy depended on the extent of dependence on nicotine as assessed by a simple questionnaire; it was 16% (7% to 25%) in "high dependence" smokers, but in "low dependence" smokers there was no significant effect. The 4 mg gum was effective in about one third of "high dependence" smokers. The efficacy of the nicotine patch (9% (6% to 13%) overall) was less strongly related to nicotine dependence, perhaps because the patch cannot deliver a bolus of nicotine to satisfy craving.**

***Conclusions*—Both gum and patch are effective aids to help nicotine dependent smokers who seek help in stopping. Among the most highly nicotine dependent smokers (those craving a cigarette on waking) the 4 mg gum is the most effective form of replacement therapy; it could enable one third to stop. In less highly dependent smokers the different preparations are comparable in their efficacy but the patch offers greater convenience and minimal need for instruction in its use. Overall, nicotine replacement therapy could enable about 15% of smokers who seek help in stopping smoking to give up the habit.**

Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, St Bartholomew's Hospital Medical College, London EC1M 6BQ
Jin Ling Tang, *research assistant*
Malcolm Law, *senior lecturer*
Nicholas Wald, *professor*

Correspondence to:
Dr Law.

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Introduction

Various forms of nicotine replacement therapy have been used to help people stop smoking. We report here a systematic analysis of the randomised controlled trials of nicotine replacement therapy,[1-39] with the objective of determining its efficacy and the circumstances in which it is most effective.

NICOTINE REPLACEMENT PREPARATIONS

Nicotine taken orally may produce indigestion and other side effects and is largely metabolised in the liver before reaching the systemic circulation. Direct absorption into the systemic circulation through the